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(54) Title: POROUS MICROCAPSULES AND THEIR USE AS THERAPEUTIC AND DIAGNOSTIC VEHICLES

(57) Abstract

Microcapsules that are porous have increased surface area. Therefore, increased loading of an associated physiologically or diagnostically–active component is possible, wherein at least a proportion of said component is present within the microcapsules and/or linked to the pores. Loading can be a factor of at least 2 greater than for corresponding non–porous microcapsules.

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POROUS MICROCAPSULES AND THEIR USE AS THERAPEUTIC AND DIAGNOSTIC VEHICLES

Field of the Invention

This invention relates to porous microparticles and to their use as therapeutic and diagnostic vehicles.

Background of the Invention

WO-A-9618388 discloses spherical microparticles, 0.1-50 μm in diameter, of cross-linked material, the microparticles being hydrophilic and capable of reconstitution in water to give a mono-dispersed suspension. The microparticles additionally comprise a physiologically or diagnostically-active agent linked directly or indirectly to the microparticles *via* free functional groups thereon.

Such microparticles can be prepared as a result of the discovery that, while microparticles having very desirable physical characteristics can be obtained by controlled spray-drying techniques, those techniques do not substantially affect functional groups. Thus, despite the heating etc. used in spray-drying, a proteinaceous material such as human serum albumin (HSA) retains functional groups such as OH, COOH, NH_2 and SH which, after cross-linking of the particles, are available for bonding to active agents. The bonded materials are useful for therapeutic or diagnostic purposes, on account of the controlled particle size that can be obtained for the particles in the spray-drying procedure. Thus, for example, microparticles of a defined size can be used for the delivery of an appropriate drug, by means of a powder inhaler, to the alveoli.

A problem with this technology, for certain active materials, is that the amount that can be bonded to the particles is low. Further, cross-linking of the microparticles may reduce the number of available bonding sites. This problem may be relatively unimportant if the agent is a highly potent drug, but even then the effect of a drug may be masked to an undesirable effect by the microparticles acting as its carrier to the site of action.

It is also possible that a predominant carrier may have a toxic effect, and/or may undesirably dictate drug release characteristics.

EP-A-0306236, EP-A-0466986, US-A-5008116, WO-A-9104732, WO-A-9300050 and WO-A-9307862 disclose various types of generally solid porous polymeric particles containing active agent retained in the pores. The agent may thus be subject, for example, to controlled release.

US-A-5069936 discloses cross-linked protein microspheres with controlled porosity, for a similar purpose. A biological agent is held on the surface and in the pores, to relative extents depending on the method of manufacture, and with a view to providing a desired degree of protection/presentation of the agent, in use.

Summary of the Invention

The present invention is based on the utility of porous microparticles, but specifically hollow microcapsules, and for a purpose different from controlled release. In particular, it has been discovered that the loading of drugs on microcapsules, of the type that can be obtained by spray-drying, can be greatly enhanced. The loading can be increased by a factor of at least 2, 3 or more, relative to the level of loading that is possible in the absence of any modification according to the present invention.

This and other desirable effects are achieved by rendering the walls of suitable microcapsules porous. The pores provide additional surface area, to which a physiologically or diagnostically-active agent can be chemically or physically linked, in addition to surface binding. The porosity may also be used as a means to introduce the agent into the microparticles. It may also enhance biodegradability.

Description of the Invention

In general, products of the invention may be prepared by the steps of producing the microparticles, fixing/cross-linking them (if necessary or desired), rendering the

microparticles porous, and then introducing the added agent. The agent may be chemically or physically linked to, trapped in, or otherwise associated with, the microparticles.

The microparticles themselves are suitably prepared by spray-drying, e.g. using the materials and techniques described, for example, in WO-A-9218164, WO-A-9609814 and WO-A-9618388. These publications also describe desirable sizes and size distributions. WO-A-9609814 and WO-A-9618388 (incorporated herein by reference) also describe agents that can be coupled to the microparticles, and various means for doing that. Cytotoxic agents such as methotrexate, cisplatin and doxorubicin are examples of such compounds that can be used in accordance with this invention.

Rendering the microparticles porous can markedly increase their surface area, provided that the pores are of sufficient size to ensure wetting of the additional surface area. Further, the thicker the walls of the microcapsules, the more opportunity exists for providing advantages such as more bound drug, and fewer microcapsules per dose. Also, porous walls should increase the biodegradation rate *in vivo*, by allowing extracellular and intracellular enzymes access to a larger surface area for preliminary breakdown. In turn, that can accelerate overall breakdown and release of bound drug.

One way of rendering spray-dried microparticles more porous involves spray-drying the wall-forming material with an additional component that can subsequently be removed from the walls, e.g. by treating the formed microcapsules with a solvent for that component. Thus, for example, a solution or suspension of a sugar such as lactose or a salt such as calcium carbonate or magnesium carbonate in HSA (used herein merely as an illustrative wall-forming material) can be spray-dried to yield microcapsules which, after heat or chemical fixation, can be treated in an aqueous medium to remove the sugar or salt. Depending on

the particle size and on the loading of carbonate suspension, the porosity/pore size is controllable.

Likewise, a porous wall may be produced by co-spraying HSA with calcium alginate, heat-stabilising the microcapsules and, in an aqueous medium, removing the alginate by Na or EDTA.

To avoid exposing unstabilised microcapsules to an aqueous phase, there is the alternative of co-spraying HSA with, say, sodium benzoate, and suspending the resulting microcapsules in ethanol to remove the benzoate. This approach may also avoid the need to stabilise the microcapsules before removal of the temporary component. Co-spraying HSA and a lipid or wax (chosen for pharmaceutical acceptability), and removing the lipid in a pharmaceutically-acceptable organic solvent, also avoids the need to fix the capsule before removing the temporary component.

Porosity may also be introduced by chemical or physical treatment of intact microparticles, fixed or unfixed. A suitable physical process comprises high energy ultrasound exposure of microcapsules suspended in a concentrated drug solution. This results in passage of the drug in solution into the central cavity. Subsequent removal of the water by, for example, lyophilisation should leave the drug within the microcapsule.

Ultrasound treatment of the microcapsules in a non-aqueous solvent, or followed by rapid transfer to a solvent, may also increase greatly the concentration of the drug in the medium, and hence the drug load entering the microcapsule. In such a case, the solvent should be pharmaceutically-acceptable, such as ethanol. Other pharmaceutically-acceptable solvents for the drug (or vehicle for suspended drug) may include lipids, particularly natural dietary components and/or naturally circulating lipids such as palmitic acid. Certain waxes with low melting point might also be acceptable and effective as carriers for dissolved or suspended drug.

Retention of a vehicle such as palmitic acid within the microcapsule may be used to affect the *in vivo* drug release rate. In place of removing the vehicle by lyophilisation etc, a filtration or centrifugation step may be used, followed by a rapid solvent wash.

Microcapsules may be loaded with bound drug and then filled with unbound drug, to increase the total drug load. The half-life for *in vivo* release may be different for bound and unbound drug, providing a burst of released (unbound) drug, followed by slower release of bound drug.

The following Example illustrates the invention.

Example

HSA was spray-dried with 0% (control), 10% and 25% lactose. The microparticles containing lactose were then stabilised by the use of heat (H) or chemical cross-linking (X), half of each type were washed (W), and all were loaded with fluorescein isothiocyanate (FITC). In the following Table, therefore, "Lac 25 X W" refers to washed, chemically cross-linked microparticles containing 25% lactose. In each case, the results of 2 different runs are provided under "spec. Reading".

The data clearly indicate that increased loading is achieved by using lactose, especially if washing is used as an intentional means of removing it. In all cases, loading is increased by a factor of more than 2, with respect to the control.

Table

Sample	Spec. Reading (μm/ml)	Mean Number Of FITC Moles Bound
Lac 25 X W	0.9126/1.3406	10.33
Lac 25 X	1.0813/0.8115	8.68
Lac 25 H W	0.3508/0.4413	3.63
Lac 25 H	0.3657/0.8008	3.51
Lac 10 X W	0.4357/0.3858	3.77
Lac 10 X	0.3047/0.2178	2.39
Lac 10 H W	0.0884/0.0940	0.84
Lac 10 H	0.0804/0.1661	0.75
HSA (control)	0.0440/0.0401	0.39

CLAIMS

1. Porous microcapsules.

2. Microcapsules according to claim 1, obtainable by co-spray-drying a wall-forming material and a material that can be removed from the capsule walls, and removing said material.

3. Microparticles according to either preceding claim, which are cross-linked.

4. Microcapsules according to any preceding claim, 0.1 to 50 μm in size.

5. Microcapsules according to any preceding claim, which have an associated physiologically or diagnostically-active component, wherein at least a proportion of said component is present within the microcapsules and/or linked to the pores in the walls of the microcapsules.

6. Microcapsules according to claim 5, wherein said component is chemically or physically linked.

7. Microcapsules according to claim 5, wherein said component is trapped.

8. Microcapsules according to any of claims 5 to 7, wherein the loading of the active component is a factor of at least two times that obtainable for the same size of non-porous microcapsules.

9. Microcapsules according to claims 8, wherein the factor is at least 3 times.

10. Microcapsules according to any of claims 5 to 9, for use in therapy or diagnosis.

INTERNATIONAL SEARCH REPORT

International Application No
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A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 A61K9/16 A61K9/50 A61K49/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

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X	EP 0 306 236 A (ADVANCED POLYMER SYSTEMS, INC.) 8 March 1989 cited in the application see page 11 - page 12; example 3.1.1. ---	1-10
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X	WO 91 04732 A (ADVANCED POLYMER SYSTEMS, INC.) 18 April 1991 cited in the application see the whole document --- -/--	1-10

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

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1

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1

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